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# C-reactive protein as a predictor of total arteriosclerotic outcomes in type 2 diabetic nephropathy

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*Background.* The inflammatory marker C-reactive protein (CRP) has been found in most, but not all, prospective studies to be associated with future cardiovascular outcomes. However, CRP has not been tested in the high-cardiovascular risk population of type 2 diabetic nephropathy.

*Methods.* We studied the independent relationship between CRP and the subsequent development of incident or recurrent arteriosclerotic outcomes (primary) and congestive heart failure events (secondary) in 1560 individuals with diabetic nephropathy, overt proteinuria, and hypertension enrolled in the prospective Irbesartan Diabetic Nephropathy Trial.

*Results.* Traditional cardiac risk factors were highly prevalent, CRP levels were high overall [quintiles (mg/L) 1st, 0 to 1.2; 2nd, 1.3 to 2.5; 3rd, 2.6 to 5.0; 4th, 5.1 to 10.0; and 5th, >10), and subsequent cardiovascular events were very common. A univariate relationship existed between CRP and total arteriosclerotic outcomes ($P < 0.0001$). However, after adjusting for study intervention and traditional risk factors, the relationship no longer remained. In fact, controlling for previous cardiovascular disease alone caused the association to become nonsignificant. The secondary analysis found a significant univariate relationship between CRP and congestive heart failure events ($P = 0.007$) that persisted in multivariate analyses ($P = 0.006$). However, this relationship was confined to the highest CRP quintile [RR (95% CI) 2.0 (1.27, 3.16)].

*Conclusion.* In diabetic patients with nephropathy, CRP does not add predictive information above and beyond that provided by traditional established risk factors. Whether this holds true for other populations with similar risk burdens is an important public health question that should be addressed. A secondary finding of a link between CRP and congestive heart failure requires further confirmation.

**Key words:** C-reactive protein, cardiovascular, arteriosclerosis, diabetes, nephropathy, Irbesartan Diabetic Nephropathy Trial.

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In recent years the role of inflammation in the initiation and progression of atherothrombosis has been intensively studied [1]. Most [2–4], but not all [5], prospective studies from population-based or selected cohorts suggest that serum concentrations of the inflammatory marker C-reactive protein (CRP) are positively associated with the development of de novo or recurrent arteriosclerotic disease, independent of traditional cardiovascular risk factors.

However, there is a paucity of data on the association between CRP levels and cardiovascular disease outcomes in chronic kidney disease (CKD) patients and, more specifically, in individuals with type 2 diabetic nephropathy. Both of these populations are at particularly high risk for cardiovascular disease events [6, 7].

We hypothesized that baseline concentrations of CRP are closely associated with the subsequent development of incident or recurrent arteriosclerotic outcomes, independent of traditional risk factors, in high-risk type 2 diabetic patients with nephropathy. This hypothesis was tested in subjects enrolled in the multicenter, international Irbesartan Diabetic Nephropathy Trial (IDNT) cohort. In addition, we performed a secondary analysis on congestive heart failure outcomes to confirm a recent population-based preliminary report that found an association between CRP levels and incident congestive heart failure [8].

## METHODS

### Population

The IDNT was an investigator-initiated, prospective, three-arm, randomized, double-masked study in 1715 patients with type 2 diabetic nephropathy that compared treatment with irbesartan, amlodipine, or placebo. Randomization occurred between March 21, 1996, and February 25, 1999 in over 200 clinical centers in North and South America, Europe, and Asia. Details of the baseline

patient characteristics and renal and cardiovascular outcomes of this study have been published [9–11]. The institutional review board or ethics committee of each center approved the protocol, and all patients gave written informed consent after reviewing a written summary of the study plan. In brief, eligibility criteria included the following: age between 30 and 70 years old; type 2 diabetes mellitus and overt nephropathy as manifested by a 24-hour urinary protein excretion rate ≥900 mg; a serum creatinine between 1.0 and 3.0 mg/dL in females or 1.2 and 3.0 mg/dL in males; and baseline blood pressures > 135/85 mm Hg or treatment with antihypertensive agents. The primary outcome of the IDNT was time to occurrence of a composite renal outcome of doubling of entry serum creatinine, end-stage renal disease (ESRD), or all-cause cardiovascular mortality. The present study was an ancillary analysis of the IDNT and included the 91% of participants in whom samples were available for determination of baseline serum CRP ($N = 1560$).

### Measurements and laboratory tests

Body mass index (BMI) was defined as weight (kg) divided by height ($m^2$). Blood pressures were taken in the seated position using standardized sphygmomanometers. Baseline samples were drawn between March 21, 1996, and February 25, 1999, and stored at −70°C. High sensitivity CRP concentrations were measured in the Vitamin Metabolism and Aging Laboratory (USDA-Human Nutrition Research Center, Boston, MA, USA). CRP concentrations were determined by a latex particle–enhanced immunoturbidimetric assay (k-ASSAY) (Kamiya Biomedical Company, Seattle, WA, USA). The intra- and intercoefficients of variation for this assay are 2.0% and 2.5%, respectively. CRP quintiles were defined as the following (mg/L): 1st, 0 to 1.2; 2nd, 1.3 to 2.5; 3rd, 2.6 to 5.0; 4th, 5.1 to 10.0; and 5th, >10. Serum creatinine, hemoglobin $A_{1c}$ ($HbA_{1c}$), lipid levels, and 24-hour urinary protein levels were measured in one of four IDNT regional laboratories using standard automated clinical chemistry techniques. Proteinuria measurements were based on the urinary protein/creatinine ratio derived from the 24-hour urine collection.

### Definition of cardiovascular outcomes

The total arteriosclerotic outcome, the primary outcome for this analysis, included all of the following [9]: cardiovascular mortality; myocardial infarction documented by clinical data such as enzyme and electrocardiogram changes; stroke documented by brain imaging or clinical deficits persisting more than 24 hours and requiring hospitalization; lower extremity amputations, and unplanned (at time of randomization) cardiac or peripheral revascularization procedures. All outcomes were ultimately adjudicated by an IDNT Outcomes Committee [11]. For the purposes of this present study we performed a separate secondary analysis on all congestive heart failure outcomes, defined as congestive heart failure requiring hospitalization or, alternatively, treatment with renin-angiotensin-aldosterone blockade.

### Statistical methods

Because the cardiovascular outcomes that we modeled (total arteriosclerotic and congestive heart failure) could occur more than once, we determined relative risks using the Anderson-Gill formulation of the proportional hazards model [12] in which patients are considered at risk for the first event from randomization to the time of the first event, at risk for the second event from the day following the first event to the time of the second event, and so forth, permitting use of all of the data. In accordance with the method of Lee, Wei, and Amato [13] we used a robust variance estimate that takes into account the possibility of correlation of risk for multiple events within each patient. Models were developed that included the randomization group and the following traditional baseline cardiovascular characteristics: age, gender, smoking history, history of previous cardiovascular disease, BMI, seated systolic and diastolic blood pressure, $HbA_{1c}$, the inverse of serum creatinine, and the total/high-density lipoprotein (HDL) cholesterol ratio. Quintiles of CRP were analyzed as ordered factors. The $P$ value of the first order (linear) component of the factor was used to test for a linear trend across the quintiles. For testing correlations between parameters and baseline characteristics, CRP and 24-hour urine protein were logarithmically transformed. Statistical analyses were performed and graphics generated using S-Plus for Windows version 6.2 (Insightful Corp., Seattle, WA, USA).

## RESULTS

Of the 1715 patients enrolled in the IDNT, 1560 had samples available for baseline CRP measurements. With the exception of BMI (30.9 vs. 29.7) ($P = 0.01$) and 24-hour urinary protein levels (3.26 g vs. 2.65 g) ($P = 0.05$), there were no significant differences between subjects who did and did not have CRP samples available. The cohort was comprised mainly of middle-aged males with a high degree of cardiovascular disease risk. Nearly half the study subjects had baseline cardiovascular disease, and most had a history of smoking, obesity, dyslipidemia, and overt proteinuria (see Table 1). Cardiovascular outcomes were followed for a mean of 2.6 years, and events were very common. The total arteriosclerotic outcome included 486 events in 361 patients, and the congestive heart failure outcome included 316 events in 205 patients.

Table 2 confirms the well-recognized correlation between CRP and BMI [14]. In addition, significant, though

**Table 1.** Baseline characteristics

| | |
|---|---|
| Total subjects | 1560 |
| Age *years* | 58 ± 8[a] (54–65)[b] |
| Males % | 66.4 |
| Baseline cardiovascular disease History % | 45.5 |
| Cigarette smokers % | |
| Never | 38.3 |
| Past | 42.1 |
| Current ≤16/day | 9.5 |
| Current >16/day | 7.5 |
| Not available | 2.6 |
| Duration of diabetes *years* | 14.7 ± 8.0[a] (9–20)[b] |
| Body mass index $kg/m^2$ | 30.9 ± 5.8[a] (26.8–34.2)[b] |
| Diastolic blood pressure *mm Hg* | 87 ± 11[a] (80–94)[b] |
| Systolic blood pressure *mm Hg* | 159 ± 20[a](145–171)[b] |
| Hemoglobin $A_{1c}$ % | 8.1 ± 1.7[a](6.9–9.1)[b] |
| Total/high-density lipoprotein cholesterol | 5.8 ± 2.2[a] (4.4–6.9)[b] |
| 24-hour urinary protein *g* | 2.27[c] (1.26, 4.0)[b] |
| Inverse serum creatinine (1/μmol/L)(1/mg/dL) | $7.5 \times 10^{-3} \pm 2.38 \times 10^{-3}$[a] ($5.66 \times 10^{-3}$ –$9.20 \times 10^{-3}$)[b] [0.66 ± 0.21[a] (0.50–0.77)[b]] |
| C-reactive protein *mg/L* | 3.4[c] (1.6–7.9)[b] |

[a]Mean ± standard deviation; [b]25th to 75th percentile; [c]Geometric mean.

**Table 2.** Correlations between C-reactive protein (CRP) and baseline characteristics

| Characteristics | *R* | *P* value[a] |
|---|---|---|
| Body mass index | 0.31 | <0.0001 |
| Hemoglobin $A_{1c}$ | 0.11 | <0.0001 |
| Total/high-density lipoprotein cholesterol | 0.08 | 0.003 |
| Systolic blood pressure | −0.00 | NS |
| Inverse serum creatinine | −0.04 | NS |
| Diastolic blood pressure | 0.01 | NS |
| Age | −0.00 | NS |

[a]NS is nonsignificant.

less clinically relevant, associations between CRP and $HbA_{1c}$ and the cholesterol ratio are also seen. Higher CRP levels were also manifested in individuals with a history of cardiovascular disease (yes, 7.0 and no, 4.9) ($P$= 0.0001) and females (females, 7.0 and males, 5.3) ($P$= 0.002), though not in persons with a smoking history.

As shown in Table 3, there was a significant univariate relationship between CRP and total arteriosclerotic outcomes. Despite the close correlation between adiposity and CRP, this finding did not change significantly even after controlling for the presence of obesity (defined as BMI >30) (data not shown). Results of multivariate analyses are seen in Figure 1 and Table 3. After adjusting for study randomization and recognized cardiovascular risk factors, the significant association between CRP and total arteriosclerotic events no longer remained. The single most explanatory parameter in this model was the existence of a prior history of cardiovascular disease [RR (95% CI) 1.75 (1.39, 2.19)]. In fact, adding this variable alone to the univariate analysis removed the significance of CRP in that model. The only other significant correlate in the total arteriosclerotic outcome model was seated diastolic blood pressure (per 10 mm Hg increase) [0.86 (0.78, 0.95)]. No interaction between CRP and kidney function was found, nor was CRP predictive of outcomes in subjects even after they were divided into quartiles by kidney function.

The secondary analysis did find a univariate association between CRP and congestive heart failure outcomes (Table 3). Interestingly, this positive relationship remained after adjustment for study randomization and cardiovascular risk factors, as shown in Table 3 and Figure 2, though it was confined to the highest quintile. Similar to the primary outcome, a prior history of cardiovascular disease was an important predictor of future congestive heart failure events, as was an abnormal serum creatinine.

## CONCLUSION

This is the first study to determine the relationship between CRP levels and subsequent cardiovascular outcomes in a representative population with overt diabetic nephropathy. CRP was not associated with the subsequent development of total arteriosclerotic outcomes in this large, multicenter cohort, independent of the effects of traditional risk factors. A secondary analysis did confirm previous preliminary findings of an association between CRP and subsequent congestive heart disease events; however, this was restricted to the highest CRP quintile [8].

Prospective information about the relationship between CRP and cardiovascular outcomes in CKD and/or type 2 diabetes is sparse. A positive association was found between CRP and hospitalizations in a small cohort of individuals with advanced CKD ($N = 66$) (20% diabetic) followed for 1 year [15]. Though 37% of the hospitalizations were cardiovascular in origin, the relationship between cardiovascular events and CRP was not specific addressed. Prospective and case-control studies analyzing this association in diabetic populations have found mixed results [16–19]. Of note, none of these studies included subjects with overt diabetic nephropathy (i.e., manifesting elevated serum creatinine levels and gross proteinuria). This distinction is important because manifestations of kidney disease from type 2 diabetes most likely reflect a more intense or chronic disease exposure, and hence a higher cardiovascular disease risk.

The acute phase reactant CRP is a marker of systemic inflammation that has been found, in most studies, to be a reliable and independent predictor of future primary or secondary cardiovascular events [1–4]. Consequently, CRP measurements have been touted as a potentially useful tool in clinical practice. However, recent prospective studies have found CRP to play a more modest or even no predictive role above and beyond that of traditional cardiac risk factors [5, 20]. Our findings are

**Table 3.** C-reactive protein (CRP) and cardiovascular event risk[a]

| Outcome | CRP quintiles[b] 1st | 2nd | 3rd | 4th | 5th |
|---|---|---|---|---|---|
| Primary: Total arteriosclerotic events | | | | | |
| Univariate ($P = 0.02$) | 1.0 [Ref] | 1.38 [1.00, 1.88] | 1.29 [0.95, 1.76] | 1.31 [0.96, 1.78] | 1.57 [1.13, 2.18] |
| Multivariate ($P = 0.38$) | 1.0 [Ref] | 1.22 [0.86, 1.72] | 1.23 [0.87, 1.74] | 1.21 [0.84, 1.73] | 1.23 [0.82, 1.85] |
| Secondary: Congestive heart failure events | | | | | |
| Univariate ($P < 0.0001$) | 1.0 [Ref] | 1.27 [0.81, 1.99] | 1.35 [0.85, 2.15] | 1.63 [1.03, 2.59] | 2.58 [1.66, 4.02] |
| Multivariate ($P = 0.006$) | 1.0 [Ref] | 1.26 [0.79, 2.00] | 1.21 [0.73, 2.01] | 1.30 [0.79, 2.14] | 2.00 [1.27, 3.16] |

[a]Controlled for study intervention and the following cardiac risk factors: age, gender, systolic and diastolic blood pressure, body mass index, presence of baseline cardiovascular disease, smoking, total/high-density lipoprotein cholesterol, hemoglobin $A_{1c}$, and renal function.
[b]Relative risk [95% CI].

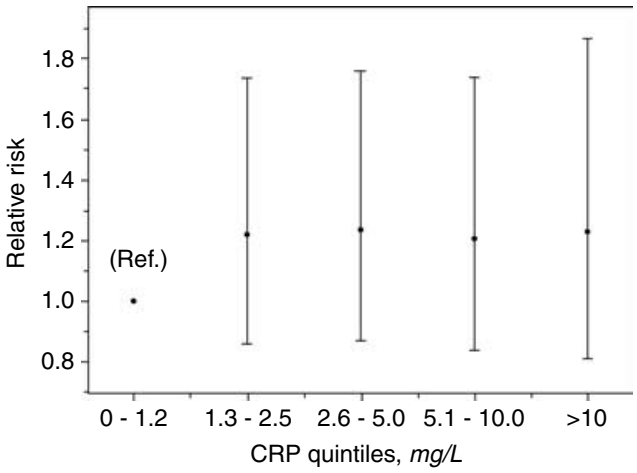


**Fig. 1. C-reactive protein (CRP) and risk of total arteriosclerotic events.** Adjusted for randomization group and the following recognized cardiovascular risk factors: age, gender, systolic blood pressure, diastolic blood pressure, body mass index, renal function, prior cardiovascular history, smoking, lipids, and hemoglobin $A_{1c}$.

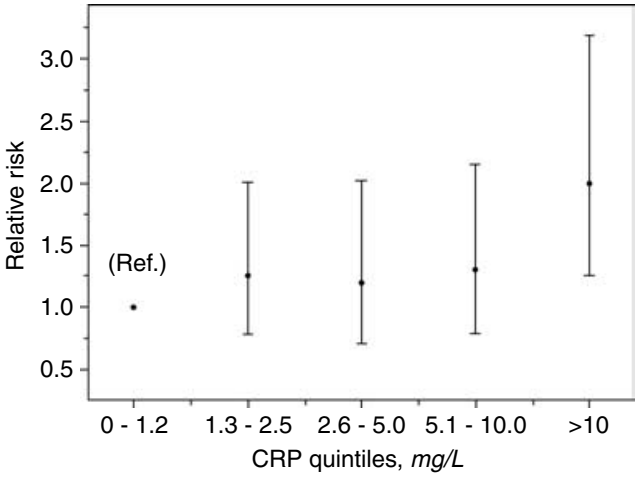


**Fig. 2. C-reactive protein (CRP) and risk of congestive heart gailure.** Adjusted for randomization group and the following recognized cardiovascular risk factors: age, gender, systolic blood pressure, diastolic blood pressure, body mass index, renal function, prior cardiovascular history, smoking, lipids, and Hemoglobin $A_{1c}$.

consistent with and extend the findings of these latter reports. Part of the lack of association may be related to an overestimation of the relationship between CRP and cardiovascular events in earlier published reports, a pattern that is often seen with emerging risk factors [21]. However, a crucial factor in our cohort is related to the particular attributes of this study population. Individuals with overt diabetic nephropathy manifest multiple cardiovascular risk factors (e.g., CKD, diabetes, hypertension, obesity, proteinuria) and consequently a very high cardiovascular rate [11, 22]. In our trial, a large proportion of participants suffered a de novo or recurrent cardiovascular event over a relatively modest follow-up period. Furthermore, as previously mentioned, the length and severity of exposure to traditional risk factors is significantly greater in our cohort compared to other diabetic populations in which CRP has been studied (hence the relatively high baseline CRP levels seen here). Consequently, it is likely that any predictive effect of CRP was simply subsumed by the heavy traditional cardiovascular disease risk burden seen in our study population. The powerful predictive value of having a prior history of cardiovascular disease as well as other traditional risk factors supports this premise. Put another way, the simple act of enquiring as to whether a study subject had a prior history of cardiovascular disease was far more predictive of future events than was a CRP level. This raises the question of whether CRP is an effective predictive tool in any population with a similarly high prevalence of traditional cardiovascular risk factors. Given the burden to patients (and the health care system) of using CRP as a standard predictor of cardiovascular risk, this issue has important public health implications. Finally, nontraditional risk factors linked to a reduction in the glomerular filtration rate but not to elevated CRP levels, such as hyperhomocysteinemia [23], may differentiate our study

cohort's risk from individuals with normal kidney function [24].

Of note, other factors sometimes found to modify CRP levels and/or cardiovascular risk, such as exercise and medications like 3-hydroxy-3-methylglutaryl coenzymeA (HMG-CoA) reductase inhibitors, were not included in this analysis [25, 26]. However, these risk factors are not "traditional" risk factors, and have not, in general, been routinely measured in other major prospective CRP studies. Certainly the former variable would be difficult to assess routinely in the clinical setting. The lack of association between CRP and arteriosclerotic outcomes should not be related to the length of patient follow-up, since data suggest that this relationship becomes weaker, not stronger, over time [21].

A secondary analysis did confirm an earlier finding in the Framingham population-based cohort that linked baseline CRP levels with future congestive heart failure events [8]. Proinflammatory cytokines have been shown to have modulating effects on left ventricular function and remodeling, as well as to alter myocyte function and apoptosis [27]. However, this association was confined to the uppermost distribution of CRP and therefore requires further confirmation in other studies.

In conclusion, our study of high-risk type 2 diabetic patients with overt nephropathy found that CRP does not add predictive information about arteriosclerotic risk above and beyond that provided by established and traditional risk factors. Whether this is true in other populations with similar risk burdens is an important public health question that needs to be addressed. A secondary finding linking CRP at the highest levels and congestive heart failure events is intriguing but requires further confirmation.

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## REFERENCES

1. Willerson JT, Ridker PM: Inflammation as a cardiovascular risk factor. *Circulation* 109 (Suppl 1):S2–S10, 2004
2. Ridker PM, Cushman M, Stampfer MJ, *et al*: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
3. Ridker PM, Buring JE, Shih J, *et al*: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 98:731–733, 1998
4. Ridker PM, Rifai N, Pfeffer MA, *et al*: Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 98:839–844, 1998
5. van der Meer IM, de Maat MP, Kiliaan AJ, *et al*: The value of C-reactive protein in cardiovascular risk prediction: The Rotterdam Study. *Arch Intern Med* 163:1323–1328, 2003
6. Sarnak MJ, Levey AS, Schoolwerth AC, *et al*: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108:2154–2169, 2003
7. Haffner SM, Lehto S, Ronnemaa T, *et al*: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
8. Vasan RS, Sullivan LM, Roubenoff R, *et al*: Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: The Framingham Heart Study. *Circulation* 107:1486–1491, 2003
9. Rodby RA, Rohde RD, Clarke WR *et al*, for the Collaborative Study Group. The Irbesartan Type II Diabetic Nephropathy Trial: Study design and baseline patient characteristics. *Nephrol Dial Transplant* 15:487–497, 2000.
10. Lewis EJ, Hunsicker LG, Clarke WR *et al*: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
11. Berl T, Hunsicker LG, Lewis JB, *et al*: Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 138:542–549, 2003
12. Anderson P, Gill R: Cox's regression model for counting precesses: A large sample study. *Ann Stat* 10:1100–1120, 1982
13. Lee E, Wei L, Amato D: Cox-type regerssion analysis for large number of small groups of correlated failure time observations, in *Survival Analysis, State of the Art*, edited by Klein J, Goel P, The Netherlands, Kluwer Academic Publishers, 1992, pp 237–247
14. Greenfield JR, Samaras K, Jenkins AB, *et al*: Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation* 22:3022–3028, 2004
15. Ortega O, Rodriguez I, Gallar P, *et al*: Significance of high C-reactive protein levels in pre-dialysis patients. *Nephrol Dial Transplant* 17:1105–1109, 2002
16. Schulze MB, Rimm EB, Li T, *et al*: C-reactive protein and incident cardiovascular events among men with diabetes. *Diabetes Care* 27:889–894, 2004
17. Curb JD, Abbott RD, Rodriguez BL, *et al*: C-reactive protein and the future risk of thromboembolic stroke in healthy men. *Circulation* 107:2016–2020, 2003
18. Mojiminiyi OA, Abdella N, Moussa MA, *et al*: Association of C-reactive protein with coronary heart disease risk factors in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 58:37–44, 2002
19. Sakkinen P, Abbott RD, Curb JD, *et al*: C-reactive protein and myocardial infarction. *J Clin Epidemiol* 55:445–451, 2002
20. Danesh J, Wheeler JG, Hirschfield GM, *et al*: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 350:1387–1397, 2004
21. Tall AR: C-reactive protein reassessed. *N Engl J Med* 350:1450–1452, 2004
22. Brenner BM, Cooper ME, de Zeeuw D, *et al*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001

23. Friedman AN, Hunsicker LG, Selhub J, *et al*: Clinical and nutritional correlates of C-reactive protein in type 2 diabetic nephropathy. *Atherosclerosis* 172:121–125, 2004
24. Friedman AN, Bostom AG, Selhub J, *et al*: The kidney and homocysteine metabolism. *J Am Soc Nephrol* 12:2181–2189, 2001
25. Castaneda C, Gordon PL, Parker RC, *et al*: Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis* 43:607–616, 2004
26. Ridker PM, Rifai N, Pfeffer MA, *et al*: Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 100:230–235, 1999
27. Baumgarten G, Knuefermann P, Mann DL: Cytokines as emerging targets in the treatment of heart failure. *Trends Cardiovasc Med* 10:216–223, 2000